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10/668,214	09/24/2003	Alan K. Smith	216499US55CONT	1574

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EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
04/01/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/668,214	SMITH ET AL.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-71, 77-80 , 84, 85, and 87- 100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66-71, 77-80 , 84, 85, and 87- 100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment filed on 02/08/08 is acknowledge

2. Claims 66-71, 77-80 , 84, 85, and 87- 100 are pending.

Claims 66-71, 77-80 and 84, 85, and 87- 10 read on method of providing immunotherapy to a patient comprising culturing human T cells in a liquid culture medium which is replaced at a rate of at least 25% daily for more than one day and transferring said cultured cells into said patient are under consideration in the instant application.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> *The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

4. Claims 66-71, 77-80 and 84, 85, and 87- 10 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of obtaining *ex vivo* T cells with enhanced replicative potential, comprising culturing said T cells in a liquid culture medium which is replaced at a rate of at least 25% daily for more than one day , does not reasonably provide enablement for a method of providing immunotherapy to a patient comprising culturing human T cells in a liquid culture medium which is replaced at a rate of at least 25% daily for more than one day and transferring said cultured cells into said patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action, mailed on 10/11/07.

Applicant's arguments, filed 02/08/08 have been fully considered, but have not been found convincing.

Applicant asserts that: (i) the specification teaches that cell that are cultured ex vivo under certain condition results in cells with enhanced replicative function, making said cells useful for therapeutic applications such as immunotherapy (ii) In Declaration under 37 CFR 1.132 DR.

Smith provides a discussion for how one skill in the art would know the correlation of T-cell proliferation potential telomere length, persistence in vivo and clinical response. In said declaration Dr. Smith further presents and explains additional data that demonstrates why the cells would be useful for therapeutic application.

Contrary to Applicant's assertion, as has been stated in the previous Office Action, the specification only discloses detailed *in vitro* studies of: (i) enhanced proliferative potential of T cells that may produce higher levels of particular cytokines on per cell basis (see Examples 1 and 2 in particular) and (ii) the enhanced ability of DC that were cultured under very specific growth condition in the alloMLR compared to dendritic cells grown under static culture conditions to stimulate T-cells (see example 3 in particular).

The Specification does not teach or even determine if said enhanced replicative potential would be preserved when said *ex-vivo* expanded T cells are transferring into a patient. The specification does not adequately teaches or provide any examples of providing immunotherapy to a patient by transferring to a patient of said T cell that were culturing *ex-vivo* under conditions wherein culture medium has been replaced at the rate of 25% daily compare to T-cells that were cultured in a static culture. Since there is no *in vivo* studies and data in the specification to show the effectively of a method of providing immunotherapy to in a patient, comprising culturing human T cells in a liquid culture medium which is replaced at a rate of at least 25% daily for more than one day and transferring said cultured cells into said patient, it is unpredictable how to correlate *in vitro* results with *in vivo* use. This, although the Specification describes certain *in vitro* experiments, there is no correlation on this record between *in vitro* experiments and in vivo use. It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to efficacy in humans or animals (emphasis added). Ex parte Maas, 9 USPQ2d 1746. Moreover, it is noted that the data disclosed in Table 1 of the instant specification compared the proliferation potential between cells that have been cultured in T-flask with cells grown in constant perusing system (CPS) . At the time the invention was made one skill in the art would know that proliferation of cells grown in these two culturing systems would be different. Cells grown in T flask would be "contact inhibited ", that decreased or arrested in cell proliferation, while cells grown in CPS would maintained cell proliferation (see for Example, Ahern, Manual for introduction to experimental cell Biology, 1992, pages 83-86 in particular). Thus, it is unclear if one skill in the art would considered it appropriate to conclude that cells grown under CPS have an enhanced replicative potential, when compare to T cells grown in T flask in static culture.
It is noted that Declaration by Dr. Smith clarify that primary cultures has been incubated by 10 days either in T flask or under CPS , then harvest and transfer in parallel to secondary cultures and to determine the respective proliferative capability. However, as has been discussed previously, one skill in the art would expect that cells grown for 10 days in T-flask would be different from the cells grown for the same period under CPS.

With regards to Declaration by Dr. Smith.

It is noted that all data provided in declaration by Dr. Smith are related to *in vitro* studies. There is no indication in said declaration that enhanced proliferative potential of T cells that may produce higher levels of particular cytokines on per cell basis would even be preserved when said cells are re-infused into the patients. Moreover, the Examiner already acknowledge that at the time the invention was made one skill in the art would well know that infusing of T cells would be useful for immunotherapy. However, as has been stated supra, it is the Examiner position , that the specification as well as the newly submitted data in declaration by Dr. Smith does not provide any evidences of any benefits for immunotherapy to a patient by transferring to patient T cell that were culturing *ex-vivo* under conditions wherein culture medium has been replaced at the rate of 25% daily compare to T-cells that were cultured in a static culture.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of providing immunotherapy to a patient, comprising culturing mature human cells in a liquid culture medium which is replaced at a rate of at least 25% daily for more than one day and transferring said cultured cells into said patient, in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 66-71, 77-80 and 84, 85, and 87- 100 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,858,358 in view of Stacey et al.(Manual of Cell Culture Techniques, 1990, pages 1-63) for the same reasons set forth in the previous Office Action, mailed on 10/11/07.

Applicant's arguments, filed 02/08/08 have been fully considered, but have not been found convincing.

Applicant asserts that the combination of US'358 and Stacey et al., does not provided the requested predictable result because the art teaches different methodologies. Neither US Patent'358 nor Stacey et al., describe or otherwise suggest replacing medium at at least 25% daily. The results as shown in the specification are unexpected and novel.

Contrary to Applicant's assertion, it has been recently stated that KSR forecloses the argument that a specific teaching, suggestion, or motivation are required to support a finding of obviousness See Board decision (see *KSR International Co v Teleflex Inc*., 550U.S.-, 82 USPQ2d 1385, 2007).

US Patent '358 teaches a method of providing a immunotherapy to a patient, comprising administering to a patient T cells that has been cultured *ex-vivo* under growth condition, wherein culture medium is replaced and wherein growth conditions results in obtaining T cells with enhanced replicative potential (see entire document, columns 12, 18, 23 and 24 in particular).

The claimed invention differs from the reference teaching in that US Patent '358 does not explicitly teach that the culture medium is replaced daily at the rate of at least 25%, 50% to 100% for the cell density from $1x10^4$ to $1x\ 10^7$ cell per ml of culture .

Stacey et al., teach a general method of culturing mammalian cells. Stacey et al., teach that culture medium should be replaced at appropriate time to allow optimal growth (see entire document, pages 21 and 24 in particular). Thus, it would require only routine experimentation for a person of ordinary skill in the art to determine the optimum rate of replacement of the medium, i.e. at a rate of 25% or 50% or from 25% to 100% . Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

All the claimed elements were known in the prior art and one skill in the art could have combine the elements as claimed by known methods with no change in their respective function and the combination would have yield predictable results to one of ordinary skill in the art at the time of the invention (see *KSR International Co v Teleflex Inc*., 550U.S.-, 82 USPQ2d 1385, 2007).

With regard to Applicant's statement that the results for T cells as shown in the specification are unexpected and novel, since conventional wisdom emphasizes splitting cultures to maintain low density.

The Examiner disagrees with said statement. As has been discussed above , at the time the invention was made one skill in the art would know that growing cells under condition wherein the growth medium is constantly perused, i.e. constantly replaced would make it possible to produce a cell culture with high cell density without the need of splitting cultures. Moreover, the fact that T cells grown under conditions wherein growth medium is replaced would have different biological function compare to cells that are cultured under static conditions would be quit expected to one skill in the art at the time the invention was made.
As had been discussed previously, in the Declaration by Dr. Smith the cells growing under static culture (0% exchange) has been compared with cells growing under condition of continuously culture exchange (12, 25, 35 and 50 % exchange) on days 7, 12 and 19. In other words, cells that were grown up to 7, 12 or 19 days without medium exchange have been compared with cells grown under condition wherein culture medium has been constantly exchange. It is well know to one skilled in the art that maintaining cells under optimal growth conditions requires medium exchange on a daily basis and at appropriate cell density. (see for example Basic Cell Culture protocols, ed. Helgason and Miller, 2005, page 219). Moreover, in the Manual of Cell Culturing techniques ed. Stacey and Hockley, 2000, page 24) it is explicitly sated that maintaining cell under optimal growth conditions can be very difficult in tradition tissue culture flasks and **failure to provide adequate changes of culture medium** and failing to passage cells at appropriate times can **cause a range of deleterious effects in the cells** that might result in changes in the characteristics of the culture which may be permanent and **alter the response of cells in bioassays or other applications** (emphases added). In other words it would be well known to one skill in the art that cells growing under static condition (0% exchane) for more than 7, 12 or 19 days would have different biological function compare to cells grown under condition of continuously culture exchange.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 66-71, 77-80 and 84, 85, and 87- 100 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 95-98,100,102,108, 110 and 112 of copending Application No. 09/027,671 for the same reasons set forth in the previous Office Action, mailed on 10/11/07.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant requested that said rejection be held in abeyance since the conflicting claims have not yet been patented.

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571/ 272-0878.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Michail A Belyavskyi/
Primary Examiner, Art Unit 1644